Control of Food-borne Pathogens in Cattle: Efficacy, Adoption, and Impact on Public Health

Joint Public Meeting on Pre-Harvest Food Safety
Sponsored by USDA/FSIS, USDA/APHIS, and USDA/ARS
USDA Center at Riverside, Riverdale, Maryland 09NOV2011
Beef Production Today

- Informed regulatory oversight and industry implementation of PR/HACCP plans have resulted in greatly improved microbial process control.

- **Impact** observed across various metrics:
  - For individuals, however, statistics are less meaningful.

- 50% decline from baseline years (CDC)
- 2.5 RGB positives/1,000 samples 2010 CY
- 0.7 RGB positives/1,000 samples YTD
Beef Production Today

• Many slaughter plants now excel at microbial process control
  – RGB positives for *E. coli* O157 at all-time low
  – Diminishing opportunities for further improvement in microbial process control during slaughter/fabrication

• Very little (or poorly defined) microbiological control of raw commodity (i.e., cattle)
  – To what extent does pre-harvest control of pathogens further *impact* process control?
Basic Premise of Presentation

• Impact = Efficacy * Adoption

  – Impact >>> Defined at various levels
    • E.g., public health or slaughter establishment etc.

  – Efficacy >>> Does the intervention work?
    • Intervention can be a practice or technology

  – Adoption >>> The extent to which the intervention is implemented across the industry
Basic Premise of Presentation

• Impact = Efficiency * Adoption
Production Systems and STEC O157

- Natural desire to focus on production practices that influence shedding
  - Efforts to date unsatisfactory
- STEC O157 co-evolved to live in ruminant gut (esp. bovine)
  - Commensal bacterium
- Worldwide distribution
  - Argentina, UK, Denmark, US, Canada, France
  - Relationship between cattle and STEC O157 is robust across many production systems

 Argentine HUS Incidence is 17/100,000. In US, HUS incidence is 1.4/100,000.
Best Practices

• Best Practices have their place

BIFSCo pre-harvest BP
  – *E. coli* Summit in 2003
    • Due for an update
  1. Clean feed
  2. Clean water
  3. Appropriate environment
  4. Relative freedom from pest

• Example of specific practices based on HACCP plans
  – SOP and 3rd-party audits
  – Progressive Beef developed and implemented by BMG
Efficacy

• Majority of efficacy data about STEC O157
  – Increasing data on *Salmonella* and non-O157 STEC

Pre-Harvest

Slaughter/Fab

In-plant PR/HACCP
plant processing aids and interventions
Efficacy

• Majority of efficacy data about STEC O157
  – Increasing data on *Salmonella* and non-O157 STEC
Vaccine Technologies

• Several vaccines trialed or proposed
  – Translation of 2 products relatively advanced

1. Epitopix/Pfizer Animal Health vaccine
  – Subunit vaccine of siderophore receptors and porin proteins (SPR)
    • Mechanism by which bacteria acquire iron

2. Bioniche Food Safety vaccine
  – Subunit vaccine based on Type III Secretion System (T3SS)
    • Includes several proteins required for enterocyte attachment and effacement
Vaccine Technologies
SRP vaccine (*Epitopix/Pfizer Animal Health*)

- Thomson et al. *FPD* 2009;6:871-7
  - 85% reduction in prevalence
  - 98% reduction in concentration

- 2010 commercial studies
  - 40% reduction in feces (2 doses)
    - Reduced number of combos of beef trimmings assoc. with positive test
  - 65% reduction on hides (1 dose)

- 2011 studies (one on-going)
  - 50 to 60% reduction in feces in completed study (Renter et al.)
  - 75% reduction in ‘high shedders’
Vaccine Technologies

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Vaccine Technologies

SRP vaccine (Epitopix/Pfizer Animal Health)

Source of Images: Doug Burkhardt
Vaccine Technologies

SRP Salmonella vaccine (*Epitopix/Pfizer Animal Health*)

78% lower prevalence of *Salmonella* $P=0.05$

Prevalence of *Salmonella*, %

<table>
<thead>
<tr>
<th>SRP Vaccine used</th>
<th>No SRP vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0</td>
<td>36.8</td>
</tr>
</tbody>
</table>
Vaccine Technologies

SRP *Salmonella* vaccine (*Epitopix/Pfizer Animal Health*)

41% reduction in prevalence from 28.3 to 16.6% \( P<0.05 \)

Prevalence of Salmonella, %

Round 1  Round 2  Round 3  Round 4

Funded by the Beef Checkoff
Vaccine Technologies

T3SS vaccine (*Bioniche Food Safety*)

- Canadian regulatory agency has reviewed data and granted a full license
  - Label indication: ‘For vaccination of healthy cattle as an aid in the reduction of shedding of *Escherichia coli* O157’

- Not yet licensed in the US
  - Conditional or full license

- Peer-reviewed publications published in respected journals support efficacy
# Vaccine Technologies

## T3SS vaccine (*Bioniche Food Safety*)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Vaccination</th>
<th>Study Design</th>
<th>Sampling</th>
<th>Outcome</th>
<th>OR</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Potter et al 2004</td>
<td>3 dose</td>
<td>Day 0, 21 and 42</td>
<td>Daily for 14 days post challenge</td>
<td>Feces</td>
<td>0.35</td>
<td>0.04</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 samples: wks 0, 3, 6, 9, 12, 15</td>
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<td>0.36</td>
<td>0.04</td>
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<tr>
<td>Peterson et al 2007</td>
<td>0 dose</td>
<td>n/a</td>
<td>7 samples: wks 0, 3, 6, 9, 12, 15</td>
<td>Feces</td>
<td>0.36</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td></td>
<td>1 dose</td>
<td>Day 42</td>
<td></td>
<td></td>
<td>0.25</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 dose</td>
<td>Day 0 and 42</td>
<td></td>
<td></td>
<td>0.27</td>
<td>&lt;0.01</td>
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<tr>
<td></td>
<td>3 dose</td>
<td>Day 0, 21 and 42</td>
<td></td>
<td></td>
<td>0.21</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td>Peterson et al 2007</td>
<td>3 dose</td>
<td>Day 0, 21 and 42</td>
<td>5 samples: wks 0, 8, 10, 13, 14</td>
<td>Feces</td>
<td>0.81</td>
<td>0.57</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>TRM</td>
<td>0.01</td>
<td>&lt;0.01</td>
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<tr>
<td>Smith et al 2008</td>
<td>2 dose</td>
<td>14 – 104 days apart</td>
<td>4 samples: 3 wks apart</td>
<td>ROPES</td>
<td>0.59</td>
<td>&lt;0.01</td>
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<tr>
<td>Smith et al 2009</td>
<td>2 dose</td>
<td>Day 0 and 32</td>
<td>3 samples: wks 11, 13, 16</td>
<td>Feces</td>
<td>0.35</td>
<td>&lt;0.01</td>
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<td></td>
<td></td>
<td></td>
<td>4 samples: wks 11, 13, pre and post shipping</td>
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<td>0.01</td>
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<td>Regional vaccination</td>
<td>TRM</td>
<td>0.69</td>
<td>0.63</td>
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<td></td>
<td></td>
<td>Feces</td>
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<td>0.01</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Hides</td>
<td>0.67</td>
<td>0.33</td>
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<tr>
<td>Smith et al 2009</td>
<td>3 dose</td>
<td>Day 0, 21 and 42</td>
<td>5 samples: wks 0, 9, 11, 13, 15</td>
<td>Feces</td>
<td>0.5</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Smith et al 2009</td>
<td>2 dose</td>
<td>Day 0 and 42</td>
<td>5 samples: wks 0, 9, 11, 13, 15</td>
<td>TRM</td>
<td>0.07</td>
<td>&lt;0.01</td>
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<tr>
<td>Moxley et al 2009</td>
<td>2 dose</td>
<td>Day 0 and 42</td>
<td>5 samples: wks 0, 9, 11, 13, 15</td>
<td>Feces</td>
<td>0.66</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 dose</td>
<td>Day 0, 21 and 42</td>
<td>5 samples: wks 0, 9, 11, 13, 15</td>
<td>Feces</td>
<td>0.34</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Allen et al 2011</td>
<td>3 dose</td>
<td>Day 0, 21 and 42</td>
<td>Daily for 14 days post challenge</td>
<td>Feces</td>
<td>0.18</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Source of slide: David Smith, UNL
Vaccine Technologies

- Compelling body of evidence
  - Aid in the control of *E. coli* O157
    - SRP and reduced concentration
    - SRP control of *Salmonella*
    - On-going studies to evaluate efficacy against non-O157 STEC

- Efficacy is imperfect but nevertheless robust across a variety of study designs
  - Dose response observed
    - Effect with fewer than 3 doses
    - Snedeker et al ZPH 2011

- Can vaccines have an **impact**?
Direct-Fed Microbia\ls

• Frequently referred to as probiotics

• GRAS (approval) for use in cattle
  – No label claim against food-borne pathogens

• Thoroughly evaluated against *E. coli* O157
  – Strain specific
  – Dose response

• Broadly adopted product
  – Nutrition Physiology Company
Direct-Fed Microbials

Strain NP51 (Nutrition Physiology Co)

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Efficacy</th>
<th>Lower 95% CL</th>
<th>Upper 95% CL</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feces 0.53</td>
<td>47%</td>
<td>0.44</td>
<td>0.63</td>
<td>&lt;0.01</td>
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<tr>
<td>Hides 0.60</td>
<td>40%</td>
<td>0.49</td>
<td>0.75</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Direct-Fed Microbials

- Compelling body of evidence showing efficacy
  - Reduces prevalence of STEC O157
    - Concentration reduced >99% in one study
      - Stephens *JFP* 2007;70:1252-5
  - Some (limited) *in vivo* data against *Salmonella*
    - Stephens et al. *JFP* 2007;70:2386-91
  - On-going field study to evaluate efficacy against non-O157 STEC

- Efficacy is imperfect but nevertheless robust across many studies and locations
  - Dose response observed

- Can direct-fed microbials have an *impact*?
Sodium Chlorate

- Enterobacteriaceae are nitrate reductase positive
  - NR is constitutive among *E. coli* and *Salmonella*
  - Reduces nitrate to nitrite to generate ATP in anaerobic conditions

- Nitrate reductase will also reduce chlorate to chlorite (a highly toxic substance)
  - Chlorite produced within bacteria
  - Leads to bacterial death

- Lacking field studies of sodium chlorate efficacy
  - Have not had regulatory authorization to use this in animals intended for human consumption
  - Field studies are prohibitively expensive

- Challenge models are very encouraging
Sodium Chlorate

- Terminal application
  - Effect temporary
- Requires FDA approval
  - Sponsor pursuing approval
Bacteriophage

- Biological control using targeted selection of lytic phage
  - Product available from Elanco Food Solutions (*Finalyse*)

- Preliminary field data on STEC O157 encouraging
  - Week-on/week-off study
  - Trim positives reduced 56% ($P=0.06$)

- Existing cocktail has efficacy against STEC O26 & O103
  - Efficacy evaluated using an *in vitro* relative killing assay

Source of Data: Patrick Mies
Bacteriophage

- EFS expanding technology platform to provide efficacy against 6 non-O157 STEC
  - Phage identified with efficacy against STEC O45 & O145
  - Phage screening underway for STEC O111 & O121

- Significant implementation
  - During warmer months

Source of Data: Patrick Mies
A variety of interventions have shown consistent efficacy

Imperfect efficacy – no silver bullet
  – Efficacy nevertheless robust across study settings/designs

Some evidence for vaccine and DFM efficacy against *Salmonella*
  – Data for non-O157 STEC in progress
  • non-O157 STEC ecology still uncertain

Can adoption of an intervention(s) have a favorable *impact*?
Basic Premise of Presentation

• \textit{Impact} = \textit{Efficacy} \times \textit{Adoption}
• Qualitative relationship of
  – Pre-harvest >>> contaminated beef >>> consumers

• Supported by empirical evidence
- Qualitative relationship of
  - Pre-harvest >>> contaminated beef >>> consumers
- Supported by empirical evidence
• Qualitative relationship of
  – Pre-harvest >>> contaminated beef >>> consumers
• Can an imperfectly efficacious intervention reduce the pathogen load to a level that is effectively mitigated by in-plant PR/HACCP plan?
Impact on Public Health

- Williams et al. *FPD* 2010
Impact on Public Health

• Qualitative and logical relationship
  – Supported by empirical evidence
  – But hard to quantify impact

• More quantitative becoming available
  – Withee et al. *FPD* 2009 – streamlined model
  – Dodd et al. *JFP* 2011 – pre-harvest to harvest *E. coli* O157 (interventions efficacy)
  – Ebel et al. *JFP* 2004 – FSIS risk assessment
Quantitative Risk Assessment

Scott Hurd Farm-to-Fork Model

- Quantitative risk assessment
  - Farm to fork with various measures of *impact*
- Pre-publication

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Reduction (prevalence)</th>
<th>Reduction (log_{10} cfu/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>40</td>
<td>0.3</td>
</tr>
<tr>
<td>B</td>
<td>60</td>
<td>0.3</td>
</tr>
<tr>
<td>C</td>
<td>80</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Quantitative Risk Assessment

Scott Hurd Farm-to-Fork Model

Number of Human Cases Decreases Due to Both Reduced Prevalence and Amount of O157 on the Carcass
Quantitative Risk Assessment

Scott Hurd Farm-to-Fork Model

Number of STEC O157:H7 Illnesses Due to Consumption of Ground Beef

Number of Illnesses

Vaccine Adoption

- Efficacy 80%
- Efficacy 60%
- Efficacy 40%
Quantitative Risk Assessment

**Scott Hurd Farm-to-Fork Model**

Number of STEC O157:H7 Illnesses Due to Consumption of Ground Beef

- At 40% adoption, increased efficacy from 40 to 80% = 9% reduction
- At 40% efficacy, increasing adoption from 40 to 80% = 19% reduction

![Graph showing the relationship between vaccine adoption and the number of illnesses](image-url)
Quantitative Risk Assessment

Scott Hurd Farm-to-Fork Model

Probability of USDA/FSIS Detecting STEC O157:H7

Vaccine Adoption

- Efficacy 80%
- Efficacy 60%
- Efficacy 40%

Probability of Detection by FSIS
Quantitative Risk Assessment

Scott Hurd Farm-to-Fork Model

Number of 10,000-lb Lots Resulting in Multiple Illnesses

Number of 10,000-lb lots

- No Vaccine
- Efficacy 60%
- Efficacy 80%
- Efficacy 40%

Number Cases in a Defined Outbreak

0 10 20 30 40 50 60 70 80

2 5 10
An Opportunity to Impact

- Farm-to-fork model quantifies expected impact of intervention
  - Model built on best available data
  - All models contain some degree of uncertainty
- The model allows us to estimate the likely impact of efficacy & extent of adoption
  - Impacts at various levels
- A poorly efficacious intervention is expected to have an impact if broadly adopted
  - Adoption may be more important than efficacy
Basic Premise of Presentation

• $\text{Impact} = \text{Efficacy} \times \text{Adoption}$
Adoption of Interventions

• The first question we should collectively and independently ask is:
  – Should we implement pre-harvest interventions?
    • No necessarily a rhetorical question

• Adoption requires a systemic behavior change
  – Co-ordinated, purposeful and informed efforts to change behaviors across a variety of sectors
    • Adoption unlikely to be successfully driven by one sector

• I believe that technological innovation is no longer the most proximate challenge
  – Adoption is the challenge before us
  – To be successful, we should understand those systemic factors that influence behavior
Adoption of Interventions

- 2 examples
- Jan et al. *JRSS* 2010
  - Decision to administer antibiotics to chronically ill cattle influenced by social norms and perceived moral obligations towards others in the system
  - More than simple economic drivers of behavior
- Cross et al. *EI* 2011
  - Specific intervention perceived as most effective
  - Yet this intervention was not viewed as very practical within the UK system
- Behavior results from a complex suite of personal and interpersonal values (i.e., social norms, moral obligations, and economics)
Adoption of Interventions

1. Identify and test situations in which producers:
   – Perceive interventions as *practical & implementable*
     • Interventions must be perceived to be implementable by those responsible for that implementation
   – Perceive adoption of interventions as *advantageous*
     • Stakeholder engagement and ownership

2. Foster productive and collaborative partnerships across the supply chain (and beyond)
   – Cost borne by 1 sector and benefits elsewhere
     • Withee et al *FPD* 2009
   – Downstream sectors may need to ‘pull’ technologies
Adoption of Interventions

3. We must **evaluate and remove/overcome barriers that reduce the likelihood of adoption**
   - Cost – not very modifiable
     • How then to overcome
   - Practicality
     • Some practices practical in certain scenarios
   - Conditional license has unintended consequences that result in real barriers to adoption
     • 60-d withdrawal, access, questions of why, etc.

• Regulatory approval process must be clear, consistent, and achievable
  - Products, even if imperfectly efficacious, must move through the relevant approval processes
Adoption of Interventions

- Successful approval provides positive reinforcement to innovators and adopters
  - ‘virtuous cycle’ of innovation, approval, and adoption of every improving technologies
• Successful approval provides positive reinforcement to innovators and adopters
  – ‘virtuous cycle’ of innovation, approval, and adoption of ever improving technologies
Adoption of Interventions

- ‘Vicious cycle’ stifling innovation and adoption
- If product does what it claims, I believe it should move forward through approval process
  - Beef industry is capable of determining if efficacy is sufficient to warrant adoption
Adoption of Interventions

- ‘Vicious cycle’ stifling innovation and adoption
- If product does what it claims, I believe it should move forward through approval process
  - Beef industry is capable of determining if efficacy is sufficient to warrant adoption
Challenges to Consider

**Unintended consequences**

- Adoption will likely require cross-sector cooperation (business partnerships)
  - Restricting or prohibiting alternative marketing arrangements will reduce opportunities for adoption
- Funnelling of higher-risk cattle to facilities a lower level of microbial process control
Challenges to Consider

Unintended consequences

- Adoption will likely require cross-sector cooperation (business partnerships)
  - Restricting or prohibiting alternative marketing arrangements will greatly likelihood of adoption
- Funneling of higher-risk cattle to facilities a lower level of microbial process control

![Diagram showing the relationship between cattle risk perception and microbial process control.](image-url)
Challenges to Consider

- Incremental improvement with long-term use of a technology

Official MN *Salmonella* Test
- 10,000 Hens per Flock
- 500 Cloacal Samples/Flock
- 50 Flocks per Year
- 25,000 Hens Tested Annually

Source: Darryl Emery, Wilmar, MN (Currently 2 – 5% positive)
Challenges to Consider

- Many advances since 1994
  - PR/HACCP
  - Variety of efficacious interventions
- Still need productive and collaborative that is inclusive of relevant stakeholders
Conclusion

• Impact = Efficacy * Adoption
Conclusion

• Impact = \textit{Efficacy} \times \textit{Adoption}

• Efficacious interventions available (or on the path to availability)
  – Imperfect but can have an impact if broadly adopted
    • Best practices viewed as prerequisites
  – Variety of platforms to suit various systems
Conclusion

- **Impact** = \( Efficacy \times Adoption \)

- Efficacious interventions available (or on the path to availability)
  - Imperfect but can have an impact if broadly adopted
    - Best practices viewed as prerequisites
  - Variety of platforms to suit various systems

- At least as (sometimes more) important than efficacy
- Should we attempt to adopt interventions?
- If so, we need an inclusive, stakeholder-driven process to productively encourage adoption
Many thanks to FSIS, APHIS, and ARS
Undersecretary Hagen and her office for invitation to speak
Many colleagues who shared ideas, information or slides for this presentation
- Mindy Brashears, Todd Brashears, and Kendra Nightingale, Texas Tech
- H. Scott Hurd, Iowa State Univ.
- Dave Renter and Morgan Scott, K State
- Todd Callaway, Robin Anderson, ARS
- Dave Smith, UNL
- Epitopix & Pfizer Animal Health, Bioniche Food Safety, Nutrition Physiology Co., Elanco Food Solutions

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